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Human-animal chimeras

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Editorial

Human-animal chimeras: circumventing rather than discussing ethical concerns comes at a price

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This issue of *RBMOnline* features a highly interesting paper on chimeras intended for human gamete production by philosopher César Palacios-González (2017). The paper breaks new ground by linking two ethically charged scientific developments. Whilst several groups are aiming to create stem cell-derived gametes through tissue culture in the laboratory (Hendriks et al., 2015), others are working on interspecies chimeras as a possible future route to obtaining human stem cell-derived organs from animals, both for research and for transplantation purposes. This involves a technology called blastocyst complementation, where human induced pluripotent stem cells (iPS) are injected into animal (e.g. pig) blastocysts that have been modified genetically to be deficient in a specific organogenetic pathway (Wu et al., 2016). Using the animal's developmental environment may be a more promising route for growing human organs than tissue culture. Although, at least in theory, human-animal chimeras might also be used for growing human gametes, this has not until now been proposed or discussed in the literature. In fact, those working on the idea of interspecies chimeras have only discussed the unintended development of human gametes in animals as something to be avoided when using this route for obtaining human organs. This avoidance might require either genetic modification of the human iPS used for chimera creation (knocking out genes contributing to gametogenesis), or the use of a targeted approach in which human adult stem cells are injected into modified animal embryos at an early in-vivo stage (Rashid et al., 2014). It is argued that such measures would be needed to make the growing of human organs in chimeric animals ethically acceptable.

As Palacios-González (2017) may be right to comment, the presumption that the very idea of human gametes growing in animals is ethically problematic seems to stand in the way of even considering whether blastocyst complementation might be an alternative to creating human gametes in the laboratory. Of course, if there are scientific reasons why this option cannot be taken seriously from the outset, it is a different matter. But were it the case, one would expect this to have been discussed in the literature. Otherwise, what we see here is a form of practical self-censorship on the part of the scientific community that is in the interest of neither science, nor society. It may seem pragmatic to proactively take account of possible societal concerns and try to work around them, but the consequence is that presumed ethical barriers to what may be important developments are taken for granted and not tested by argumentation. With regard to the ethics of growing human gametes in chimeric animals, the question should be whether any possible concerns amount to valid reasons for not pursuing this route. In his contribution to this issue, Palacios-González convincingly argues that this ethical case cannot be made, at least with regard to creating human oocytes for research purposes. The issue is a pressing one, as human eggs for basic, fertility, and stem-cell research are in short supply. Many experiments that require their use cannot be carried out at present, and so the potential benefits that could emerge from such experiments are either delayed or never materialise. This state of affairs is problematic for scientists and patients worldwide.

Of the four possible counterarguments against the use of this technology for producing human oocytes that Palacios-González considers, the most challenging objection is animal welfare. Here, the ethical argument depends on considerations of proportionality (balance of benefits and harms) and subsidiarity (the requirement that there are no alternative ways to obtain the expected benefits). Although the subsidiarity requirement is being met at the moment, this may change if efforts to create human oocytes *in vitro* prove successful. It therefore remains important to also pursue that alternative. With regard to proportionality, it should be noted that in his paper Palacios-González limits himself to discussing oocyte creation for research purposes, further specifying this as research that can be expected to lead to therapies that would save human lives or reduce human suffering. But what about using animals for creating human gametes intended for reproduction? Here the assessment of proportionality would require further discussion of whether the aim of helping people to have their own genetic offspring is of sufficient moral weight to justify the inevitable infringement upon animal wellbeing. On the 'harms' side, further fine-tuning of the argument will depend on which animal species is most suited as host.

Palacios-González's paper can be read as a timely warning to governments and regulators not to follow the suggestion to only allow

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human organ or tissue creation in chimeras on the condition that no animals capable of developing human gametes will be produced, as this would block a possibly fruitful and ethically acceptable route to overcoming the present shortage of oocytes for medical research. The fear that mating by these animals might otherwise lead to hybrid or human conceptuses in animal wombs does not require this condition, as their mating can be easily prevented. Interestingly, the same line of argument (no unnecessary barriers to scientific development) can be used to question a second condition proposed by the pioneers of the organ creation scenario. This concerns the possibility that human cells would contribute to brain development in the chimeric animal. The hypothetical scenario that this would lead to an animal with human cognitive capacities created to serve as a mere source of organs or tissues would certainly raise ethical red flags. Palacios-González rightly observes that if objections based on 'dignity' have any leverage it must be with regard to this scenario. In order to preempt concerns about this, he supports the proposal to preclude the generation of human brain cells through genetic modification of the human iPS used for blastocyst complementation (Rashid et al., 2014). However, the wisdom of making this a condition without further argument can be questioned on similar grounds as put forward in his paper with regard to excluding gamete creation.

How realistic is it to suppose that even an intended colonization of animal brain development by human cells would lead to a being with human cognitive capacities? Commentators have pointed out that even if human neural progenitors were to take over, the full development of human neural structures would require larger skulls and longer gestation periods than are found in mice or pig (Bourret et al., 2016; Karpowicz et al., 2005). If this is the case, imposing the 'no-contribution-to-brain-development' condition might make important potential research applications impossible for no good reason. One might perhaps think here of developing human brain disease models in mice, for instance to study amyotrophic lateral sclerosis or other neurodegenerative disorders. If this research is blocked to address concerns about a scenario that is not just hypothetical but completely unrealistic, the same conclusion would seem to follow as with regard to ruling out gamete development in chimeras. The least one should say is that before imposing such conditions, a careful discussion of the implications is required.

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